EXPOSURE ASSESSMENT FOR FENOXAPROP-ETHYL

VOLUME II

EXPOSURE ASSESSMENT DOCUMENT

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ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN FENOXAPROP-ETHYL

BY

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EXECUTIVE SUMMARY

Fenoxaprop-ethyl is currently under review for possible registration in California as a selective post-emergent rice herbicide. Anomalies in fetal rats and liver toxicity in adult laboratory animals dosed with this chemical prompted the risk assessment for fenoxaprop-ethyl. Exposure to fenoxaprop-ethyl for workers mixing, loading, and applying (including cleanup) Whip® 1EC Herbicide with ground boom equipment to soybeans ranged from 0.42-27.2 mg per workday. Occupational exposure to workers involved in the aerial application of fenoxaprop-ethyl to rice experienced an estimated 2.32-18.80 mg of exposure per workday. Absorption data from a human study is not available. Seventy-three percent of a dermal dose of 2.3 µg/cm² in rats was considered absorbed after a 10-hour exposure period. The estimated absorbed daily dosage for workers applying fenoxaprop-ethyl with ground equipment was 1- 22 µg/kg of body weight and 2.9-52 µg/kg of body weight for workers making aerial applications.

Two major metabolites, benzoxazol mercapturic acid and a hydroxy-phenoxy propionic acid were detected in the urine of rats with a 14C labeling technique. An extensive discussion, both pro and con, is provided in this document with respect to the usefulness and limitations of applying biomarkers for estimating the absorbed dose for this herbicide in humans.

PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of a pesticide can determine its rate of absorption by the skin and how extensive it is metabolized by the human body.

Chemical Family	aryloxy-phenoxy-propionate derivatives	
Chemical Name	($\pm$)-ethyl 2-[4-[(6-chloro-2-benzoxazolyl)oxy]-phenoxy] propanoate	
Common Name	fenoxaprop-ethyl	
Trade Names	Whip®, Whip® 3600, Acclaim®, Depon® Excel®, Furore®, Option®, Option® 110, Bugle®, Cheyenne TP® Horizon®, Tiller®	
CAS Number	66441-23-4	
Empirical Formula	$C_{18}H_{16}ClN0_5$	
Molecular Weight	361.8 daltons	
Melting Point	80-85 °C	
Boiling Point	>300 °C @ 760 mm Hg	
Stability	Half-life - aqueous media (pH 9) @ 20 °C = 2.4 days	
Solubility @ 25°C	water	0.8 - 0.9 mg/kg
	toluene	>300 g/kg
	acetone	>500 g/kg
	ethyl acetate	>200 g/kg
	cyclohexane, ethanol, octanol	10 g/kg,
Appearance	Colorless solid	
Vapor Pressure	19 nPa @ 20 °C; 3.2×10^{-8} mm Hg @ 25 °C	
K_{ow}	19,200 (log K_{ow} = 4.28)	
pH	5.4 ± 1 (1% suspension, distilled water)	

REGULATORY HISTORY INCLUDING EPA STATUS

Fenoxaprop-ethyl containing products are currently registered conditionally by the US EPA in accordance with FIFRA section 3(C)(7)(C). Fenoxaprop-ethyl is not registered for any use in California. However, Whip®, a rice herbicide, is currently under review as the first section three registration of this active ingredient in California.

TECHNICAL AND PRODUCT FORMULATIONS

Whip® 1EC Herbicide is an emulsifiable concentrate formulation of fenoxaprop-ethyl that contains 1 pound of active ingredient (a.i.) per gallon, i.e. 12.5% fenoxaprop-ethyl and 87.5% inerts.

USAGE

The supplemental label for the proposed registration of Whip® 1EC Herbicide in California permits the post-emergent control of annual grasses in rice. This product can be applied by ground or air equipment but may not be applied with irrigation water. The maximum application rate for rice is 3.2 ounces of active ingredient (a.i.) per acre with a maximum of 4.8 ounces of a.i. per growing season. The proposed label requires applications to be made with a minimum of 10 gallons of water per acre to obtain thorough coverage. Whip® 1EC Herbicide is registered for use in other states for selective post-emergent control of annual and perennial grasses in rice, wheat, soybeans, cotton, peanuts and acreage conservation reserve (set-aside).

LABEL PRECAUTIONS/PERSONAL PROTECTIVE CLOTHING

The Whip® 1EC Herbicide label carries the signal word, "WARNING", with the following precautionary statements:

> "May cause substantial but temporary eye injury. Do not get in eyes. Avoid contact with skin or clothing. Harmful if swallowed, absorbed through skin or inhaled. Do not take internally. Avoid inhalation of vapor or spray mist. Remove contaminated clothing and wash before reuse."

The precautionary statements indicate the category II toxicity classification is due to the temporary eye injury that is reversible within 7 days. The statements for oral, inhalation and dermal exposure indicate these routes have a toxicity category III classification.

The latest proposed label for Whip® requires the following protective clothing to be worn: (a) pilots - long-sleeved shirt and long pants, shoes and socks, chemical resistant gloves and protective eyewear; (b) mixer/loaders - long-sleeved shirt and long pants underneath a chemical resistant suit, shoes and socks, chemical resistant gloves, and protective eyewear; (c) flaggers long-sleeved shirt and long pants, shoes and socks, chemical resistant gloves and protective eyewear.

WORKER ILLNESSESANJURIES

Since this product is not registered in California, there are no available data regarding exposure related illness reported in California.

DERMAL IRRITATION/SENSITIZATION

Fenoxaprop-ethyl has a low acute mammalian toxicity. It is classified as a category II eye irritant. The label requires eye protection and impermeable rubber gloves to be worn by workers when handling this product. A dermal sensitization test conducted with guinea pigs did not indicate this product is an animal dermal sensitizer (Jung and Weigand, 1982).

DERMAL ABSORPTION OF FENOXAPROP-ETHYL

Labeled ^{14}C-fenoxaprop-ethyl (98% radiopurity, chlorophenyl ^{14}C labeled) was prepared as a homogeneous suspension and applied dermally to four groups (20 animals per group) of female rats (Laveglia *et al*., 1986). Each dose was applied within a rubber ring encompassing 10.8 cm², which was cemented to a shaved area of skin. After application of the dose, a cover of filter paper was cemented in place on the rubber ring to cover the application site. The dermal dose applied to each group was 2.3, 23, 231, and 2315 µg/cm², respectively. The lower doses were administered as a known amount of the test substance mixed with the blank EC formulation and then diluted with water. The highest dose, however, was administered without the water dilution. The animals were individually placed in metabolic cages for urine and fecal collection and sacrificed after 0.5, 1, 2, 4, or 10 hours of exposure. Another group of rats (8 animals) was exposed to the highest dose level for 10 hours before removal of the dose by washing. These rats were kept an additional 24 or 72 hours and their excreta collected until sacrifice.

The skin washing after the 10-hour exposure period removed an average 24% of the dose in all dose groups (range 19-60%). Although radioactivity appeared in the urine as early as 0.5 hour after the dermal exposure to fenoxaprop-ethyl began, the amount of radioactivity in the excreta did not increase substantially over time for those groups sacrificed at 0.5-10 hours. After 10 hours of exposure, less than 2% of the dose was detected in the excreta of these treatment groups. Rats sacrificed 24 hours after washing the 2315 µg/cm² dose excreted approximately 1.2% of the dose. However, for those rats held 72 hours after washing the 2315 µg/cm², 12% of the dose was detected as fenoxaprop-ethyl equivalents in the excreta. The significant increase in the percentage (5.9%) of the dose excreted in the feces, 72 hours after washing the dose, suggests that either prolonged dermal absorption or enterohepatic circulation was taking place.

The amount of fenoxaprop-ethyl absorbed from a dermal application was defined as the sum of the fenoxaprop-ethyl equivalents present in various tissues (blood, internal organs), the excreta, the carcass and the bound skin residues present at the application site. The equivalents detected at the application site accounted for more than 90% of the material considered absorbed for most groups of rats. Data from the observations of rats sacrificed at 24 and 72 hours after the dose was washed off, indicate the bound skin residues continue to migrate into the body and therefore must be considered bioavailable. The percent of the dose absorbed (in parenthesis) at various dose levels 10 hours after dosing the rats was found to be: 2.3 µg/cm² (73%); 23 µg/cm² (62%), 231 µg/cm² (43%); and 2315 µg/cm² (70%) (Table 1).

This phenomenon is not normal. The lowest and highest dose (a span of one thousand fold) were absorbed at almost the same rate (73 and 70%). It is usually observed in dermal absorption studies that the percent of absorbed dose decreases as the amount of dose increases when the exposed skin area is kept constant. The study authors hypothesized this phenomena was due to the disparity in the adjuvants used to dissolve the test material. The highest dose was administered with an organic solvent-based formulation, which tends to accelerate dermal penetration as compared to a water-based emulsion applied to the rest of the treatment groups. The other plausible explanation, though unlikely as a major contributory factor, is the potential disparity in the amount of radioactivity removed through the washing procedure.

Seventy-three percent of the low dose (2.3 µg/cm²) was considered absorbed and bioavailable after a 10-hour exposure period. This rate included the percentage of a dermal dose that was bound to the application skin site. Without additional excretion data that could identify the fate of the bound-skin residues over time and the observation that fenoxaprop-ethyl equivalents continue to be excreted after 24 hours, the assumption has to be made that the bound-skin residues will ultimately be bioavailable. In the absence of human absorption data, this 73% absorption rate will be used as the human dermal absorption rate. It was derived from the lowest dosage rate, which is closest to the estimated rate of occupational exposure.

An asymptotic extrapolation of the excreted dose via an iterative process over time was attempted with the excretion data to determine the ultimate fate of the bound skin residues (Thongsinthusak, 1994). This procedure allows the direct computation of the absorbed dose from the excreted dose, and thus, the skin-bound residues can be disregarded. However, this extrapolation technique is not applicable to this study because of the very high dose administered to the test animals and the excretion of the fenoxaprop-ethyl metabolites was not complete at 72 hours.

It is known that the dermal absorption capacity of rats for many chemicals far exceeds that of man. It has been observed that rats can dermally absorb pesticides at rates 4-16 fold greater than humans exposed to the same pesticides (Wester and Maibach, 1993; Wester *et al.,* 1989; Shah *et al.*, 1981). The pharmacokinetics of chemical absorption and disposition processes dictates the target organ concentration, which in turn determines whether a threshold adverse effect, i.e. hepatotoxicity will or will not occur. For a chemical that is released very slowly through the dermal route of exposure and assuming a non-cancer endpoint, the overt toxic effect may not be manifested because the threshold dose cannot be reached at any point during or after the exposure. Since the absorption from skin-bound fenoxaprop-ethyl is a very slow process, there is a continuous disposition of fenoxaprop-ethyl equivalents (tissue distribution, biotransformation and excretion). However, the kinetics of the dose distribution to the tissues and organs after the exposure is most critical. At 10 hours post exposure, the amount of radioactivity (expressed as nanograms per gram of wet tissue) was the highest in liver, kidneys and blood. The concentration patterns and the distribution of the absorbed dose to the target organs may be compared to the adverse effect seen in various studies.

METABOLISM OF FENOXAPROP-ETHYL

There are eight reports on fenoxaprop-ethyl metabolism in mammals on record. These studies were conducted at Hoechst Agricultural Laboratory in Germany. Five of the eight reports were reviewed to identify potential urinary metabolites (Figure 1) for possible worker exposure biomonitoring and to ascertain the feasibility of applying the established analytical methods. The laboratory reports issued by the registrant described in great length the analytical techniques used in the isolation and identification of metabolites.

The first study conducted by Dorn *et al. (1982)* includes orally administered ^{14}C fenoxaprop-ethyl to female rats at 40 mg/kg and monitoring urinary and fecal excretion for metabolites at 24-hour intervals. The rates of excretion of the radioactivity in the urine and feces were measured with a liquid scintillation counter. The metabolites were separated and purified through thin-layer chromatography (TLC) and high pressure liquid chromatography (HPLC). GC-MS methodology was used to identify the structure of the parent/metabolites by reference to synthesized standards. The amount of radioactivity excreted via urine and feces was high; over 75% (combined) of the dose excreted by 48 hours and over 95% by 168 hours after dosing.

The second study (Dorn *et al*., 1985) includes oral dosing of both male and female rats at a single dose (2-10 mg/kg), or multiple dose (2 mg/kg) with ^{14}C labeled fenoxaprop-ethyl (98% radiochemically pure and labeled at chlorophenyl U ^{14}C position). In the multiple dosing regimen, 14 daily doses of unlabeled fenoxaprop-ethyl were given to rats followed with a pulse of ^{14}C-labeled fenoxaprop-ethyl on the 15th day. The objective of this study was to discern sex and dose effects, if any, on the metabolism of fenoxaprop-ethyl.

In the third study (Burkle *et al.*, 1985), dioxyphenyl-^{14}C ring-labeled fenoxaprop-ethyl (96% radiochemically pure) was applied orally to rats at 2 and 10 mg/kg dose levels. This study was designed to investigate metabolic pathways using various ring-labeling techniques. A fourth study (Dorn *et al.*, 1984) was a comparative investigation on the metabolism of orally dosed ^{14}C fenoxaprop-ethyl in various animals. This research included a group of pregnant rats that received 50 mg/kg of fenoxaprop-ethyl between day 7 and 16 of organogenesis. Also included were pregnant rabbits (50 mg/kg) and one pregnant Cynomolgus monkey (10 mg/kg). The final study (Kellner and Eckert, 1984a) entailed the oral dosing of rats for 14 days with unlabeled fenoxaprop-ethyl at 2 mg/kg body weight followed by a single dose of 2 mg/kg of body weight of ^{14}C-labeled fenoxaprop-ethyl. The rate of excretion of the dose in the urine and feces and the deposition of the dose in the organs and tissues was determined.

At a dose level of 2 mg/kg administered orally to male and female rats, the percent of the dose excreted as ^{14}C equivalents of fenoxaprop-ethyl after 96 hours was 42.1-53.9% in the urine and 33.8-40.4% in the feces (Dorn *et al.,* 1985). The postulated metabolic pathway is shown in Figure 1. The mercapturic acid is a major metabolite and amounts to approximately 14.6-26% of a given dose in rats (Dorn *et al.,* 1985). The other major metabolite, a hydroxy-phenoxy propionic acid can be detected in the urine of rats (27.5-49.6%) when the dioxyphenyl ring is labeled with ^{14}C (Burkle *et a*l., 1985). Five minor metabolites including the free acid, 2-(4-(6chloro-2-benzoxazolyloxy)-phenoxy)-propionic acid, the hydroxy isomers (4 and 5-6-chloro-2, 3-dihydrobenzoxazol-2-one), the benzoxazol (6-chloro-2, 3-dihydro-benzoxazol-2-one) and a thio compound (6-chloro-2,3-dihydrobenzoxazol-2-thione) were identified in small quantities, each representing 2-7% of a given dose (Dorn *et al.,* 1985).

The elimination of fenoxaprop-ethyl and/or its radiolabeled metabolites in the urine and feces of rats was biphasic, regardless of the sex of the animals (Kellner and Eckert, 1984a). The biological half-lives for the rapid phase I ranged from 8.5 to 12.5 hours (urine and feces). For the slower phase II, half-lives were 41-73 hours for urine and 27-34 hours for feces.

Approximately 66% of the total radioactivity was extractable from the feces with the rest remaining uncharacterized. The recovery of the dose from the feces which represented unchanged fenoxaprop-ethyl was estimated at 12%. The major metabolite (8-22%) was identified as the free acid. Other moieties were unidentifiable.

With respect to the effect of sex and varying treatment regimen on metabolism, there were no qualitative differences discerned in the excreted metabolites. However, there may be quantitative differences with respect to certain chemical species of metabolites being biotransformed and excreted. Notably, when female rats were given a single oral dose of 10 mg/kg of fenoxaprop-ethyl, or a repeated low dose of 2 mg/kg of fenoxaprop-ethyl, the excretion of the free acid was increased with a corresponding decrease in the mercapturic acid (Dorn *et al*., 1985). The metabolites identified in the urine and feces of pregnant rats receiving fenoxaprop-ethyl throughout organogenesis did not differ qualitatively from those observed in other groups of rats (Dorn *et al*., 1984). Since the dose administered was high (50 mg/kg) the amount of free acid was increased (21%), with a corresponding decrease of the mercapturic acid metabolite (10%).

The residue concentrations of fenoxaprop-ethyl and its metabolites in the tissues and organs were measured seven days after oral dosing at 2 and 10 mg/kg (Kellner and Eckert, 1982, 1984a, 1984b). The total residues at day seven ranged from 2.2 to 5.1% of the dose, irrespective of the dosages given which indicates a long tissue half-life. The residual metabolites were found in adipose tissues and excretory organs such as kidneys.

In the multiple species of pregnant animals studied, a similar pattern of metabolism was observed in all animals (Dorn *et al*., 1984). Quantitative differences exist with respect to biotransformation rate and tissue deposition of the three species. Tissue deposition pattern was observed to be in the following order: rat>rabbit>monkey.

Theoretically, since the two major urinary metabolites, namely the benzoxazol mercapturic acid and the hydroxyphenoxy propionic acid may constitute over 50% of an administered dose, potentially, they may be used as biological in markers for urinary monitoring. Because of the slow excretion of metabolites (slow phase) and the possible interferences with endogenous polar metabolites, the isolation and identification of these metabolites is perceived to be difficult. Kinetic studies on the urinary elimination half-lives of fenoxaprop-ethyl in female and male rats indicate they span a range from 41 to 73 hours. This suggests the biomonitoring period should be a minimum of four days post exposure to maximize the total recovery of metabolites from urine.

WORKER EXPOSURE

The proposed registration for Whip® 1EC Herbicide on rice is to control grassy weeds early in the growing season. Applications can be made when the rice has 5-7 leaves (25 days after planting) until panicle initiation (60 days after planting). Since fenoxaprop-ethyl acts primarily as a contact herbicide, the rice fields need to be drained or at least the water level lowered to expose the target foliage. The proposed label allows applications to be made by ground and aerial equipment. Most of the treatments will be made by aircraft due to the ease of application and the narrow use season (mid-May to mid-June) permitted by the label. However, ground equipment may be used to make spot treatments along roads and canal banks and to treat rice fields located next to sensitive crops (corn and sorghum) and environmental areas where aerial applications may cause drift problems.

GROUND APPLICATION

A worker exposure study was conducted in by Orius Associates, Inc. (1985) on behalf of the American Hoechst Corporation. Three workers at the American Hoechst Corporation field research station in Leland, Mississippi served as volunteers to apply fenoxaprop-ethyl 1EC herbicide (1.0 lb fenoxaprop-ethyl/gal) with a ground boom tractor to soybeans for 1 day each. Each worker was monitored for exposure with dermal dosimeters and personal air pumps, while performing the tasks of mixing/loading, application and cleanup of the tractor. The herbicide (EPA Registration No. 8340-EUP-7) was supplied in 5-L metal containers with integrated pouring spouts. Fenoxaprop-ethyl was applied at the maximum label rate of 0.20 lb a.i./acre with 30 gallons of water. No adjuvants or other pesticides were used. During spraying, a record was kept of the wind speed, wind direction, temperature, relative humidity, and cloud cover.

The typical workday consisted of filling the tanks with water at the station, measuring and loading the herbicide, and spraying until empty. Tanks were refilled with water from a nurse tank at the field and the tasks were repeated. For maximum exposure, all workers drove tractors equipped with only a roll bar cage and roof. The three workers applied 6-8 tank loads each for the workday that was monitored. They handled an average of 9.8 lbs of fenoxaprop-ethyl per day and treated an average of 49 acres. All the sprayers were cleaned after the last application of the day. The duration of the workday (mix/load, apply and clean) ranged from 8-11 hours.

Exposure to the body was estimated by way of a multilayer dosimeter, which allowed the estimation of potential exposure, as well as the determination of the efficacy of various layers of clothing in preventing dermal exposure. These dosimeters consisted of a cellulose glassine backing covered with one to three layers of 100% cotton or polyester/cotton material to represent various regimes of protective clothing. These layers were then, encased in a waterproof vinyl plastic "badge holder" with a 40-cm^2 open window to allow exposure. The dosimeters (total of 11) were taped to the work clothing or Tyvek® coveralls worn by the workers at the following locations; head, chest and back, both shoulders upper arms, both forearms, left and right thighs and on both lower leg/ankles.

Exposure to the hands was measured as the total residues present in the hand rinses. Each hand was vigorously triple-rinsed in 750 ml of 10% (v/v) isopropyl alcohol in distilled water. For the first replication of the mixing/loading and spraying work tasks, each worker wore impermeable gloves; neoprene by Worker A on Day 1, or polyvinyl chloride (PVC) type by Workers B and C on Days 2 and 3. The outside of each glove was rinsed and each hand was rinsed for each task. The subsequent replications of the work tasks were conducted with the workers working barehanded.

Inhalation exposure was measured by sampling the air in each worker’s breathing zone with two MSA Fixt-Flo® personal air pumps. Charcoal tube traps were used at air flow rates of 0.5 L/min for one pump and 1.0 L/min, the maximum recommended by MSA, for the other pump. Different sampling strategies were used to assess the amount of dermal and inhalation exposure. Sampling periods included a half day, full day, and the durations of the tasks of mixing/loading, spraying, and cleaning-up. Exposure was partitioned into dermal exposure for each part of the body and inhalation. Exposure was estimated for workers wearing only long pants and a long-sleeved shirt with a T-shirt. In addition to this work clothing, the proposed Whip® 1EC Herbicide label requires workers mixing this product to wear impermeable rubber gloves and goggles or a face shield.

Residues of fenoxaprop-ethyl were extracted from the monitoring media with toluene and measured by gas chromatography. All residue values were adjusted for recoveries from samples fortified in the field. In order to pool results for statistical purposes and to compare the exposures of different workers, all exposures were standardized to a rate of µg a.i./person/lb a.i. handled in the monitoring period.

The occupational exposure for the three workers is summarized in Table 2. Each value represents the µg of fenoxaprop-ethyl exposure per pound a.i. of fenoxaprop-ethyl applied for one full workday for each operator. The greatest exposures occurred to the unprotected hands, which accounted for approximately 97% of the exposure for workers, mixing, loading and applying fenoxaprop-ethyl. This high percentage is due in part to operator C who was exposed while repairing a broken line on the belly tank of the spray tractor. The Average Daily Exposure (dermal and inhalation) for the three operators was 10 mg/workday: By comparing the hand exposures with or without gloves, it was observed that wearing neoprene or PVC gloves reduced exposure by 94%. When gloves were worn, exposure of the hands still contributed significantly to total exposure. Based on task-related samples, exposure was greatest during mixing/loading, followed by spraying and clean up.

AERIAL APPLICATION

The majority of the applications for the proposed Whip® 1EC Herbicide registration on rice will be made by aircraft. The use of the ground application exposure study for fenoxaprop-ethyl as a surrogate for aerial application is not suitable. During aerial application, the work tasks are separate with the pilot as the applicator and another worker as the mixer/loader. Also, aircraft are capable of treating much larger acreages and the mixer/loader will handle greater amounts of active ingredient. An exposure study of the aerial application of Londax® herbicide (bensulfuron methyl) with a dry flowable formulation was used to estimate the exposure to workers when fenoxaprop-ethyl is applied by air because of similarities in use practices and application rate.

Two studies were conducted concurrently by Jensen and Merricks (1991) with aerial applicators located in the Sacramento Valley. The workers of two companies were monitored for dermal and inhalation exposure during the application of bensulfuron methyl at three different sites. The spray crews, consisting of a mixer/loader, pilot and flagger applied five-ten (average eight) loads of bensulfuron methyl per workday, treating approximately 60 acres per load. Bensulfuron methyl was applied at the rate of one ounce of active ingredient (a.i.) per acre with five gallons of water. Some applications were made at a higher dilution rate to enhance coverage. A total of 80 tank loads were applied during the ten workdays. The average exposure time per workday for the application personnel was: pilots-3.2 hours, mixer/loaders-3.2 hours and flaggers-3.0 hours. At the conclusion of the bensulfuron methyl applications, the pilot for each aircraft was monitored for dermal and inhalation exposure (approximately 2 hours) while performing the extensive cleaning activities required for the removal of bensulfuron methyl residues from the aircraft.

Dermal exposure for the workers was monitored with a long sleeved T-shirt (cotton) and long underwear (cotton blend) worn underneath their work clothing (coveralls, shoes and socks). In addition, the mixer/loaders wore rubber gloves and the pilots wore cotton or leather gloves. Exposure to the hands was monitored with a hand wash made with 500 ml of an aqueous detergent solution in a gallon Ziploc® plastic bag. The face and neck were wiped thoroughly with a cotton cloth saturated with a detergent solution. Inhalation exposure was monitored with a personal sampling pump attached to the worker. Air samples were collected by drawing air from the breathing zone at the rate of 2 liters/minute through two polyurethane foam filters. The pumps were operated only during the actual pesticide handling periods.

The results from analysis of the spiked/control samples indicate the analytical methodology was appropriate and the experimental values observed were reliable. The recoveries from the lab spiked sample matrices were greater than 90% over a range of fortification levels with the exception of the polyurethane foam plugs (76-97%) and one hand wash sample (89.9%). The mean rates of recovery from the matrix samples spiked in the field at the three sites were greater than 90% for all sample media with the exception of the T-shirts (89.4%). Residues were not detected on any of the control samples taken in the field. The results from the storage stability study indicate the bensulfuron methyl residues were stable in the experimental matrices. Recovery of the lab-spiked samples was greater than 95% after 90 days of frozen storage. The average recovery of bensulfuron methyl from the spray tank samples was 83.6% for the minimum dilution rate of one ounce a.i. per five gallons of water.

Dermal exposure was expressed as the residues detected per cm^2 of skin surface area or in the hand wash solutions per pound of a.i. applied. If residues were not detected for a particular sample, then one-half the detection limit for the particular sample medium was used to derive an exposure value. The results were reported as the exposure (dermal and inhalation) to bensulfuron methyl incurred per pound of a.i. applied multiplied by the total pounds of a.i. applied per workday (Table 3) to derive a total daily exposure.

The spray crews (mixer/loader, pilot and flagger) at the three sites did not work equivalent workdays. The amount of bensulfuron methyl applied and exposure time per workday varied from site to site. The spray crews applied from 20.8-33.6 lbs of bensulfuron methyl per day treating approximately 333-538 acres of rice. The appropriate method for expressing this variability is to normalize the exposure as µg of exposure per pound a.i. applied. Table 3 summarizes the inhalation and dermal exposure to the various body regions for mixer/loaders, pilots and flaggers involved in the application of bensulfuron methyl. Each value represents the average exposure in µg per pound of a.i. handled from 3-4 replicates (workdays) at each site. The greatest dermal exposures occurred to the arms of the workers: mixer/loaders-41.9 µg/lb a.i., pilots-25.0 µg/lb a.i. and flaggers-32.7 µg/lb a.i. Some workers rolled their coveralls up to their elbows while performing the work tasks, exposing the long-sleeved T-shirt dosimeters. This work practice may be due to the high temperatures (range 92-96 ^{o}F) that occurred during part of the study. Exposure to the hands of all the workers was less: mixer/loaders- 18.8 µg/lb a. i., pilot- 11.5 µg/lb a.i. and flaggers-10.7 µg/lb a.i. Inhalation exposure was minimal for all work tasks with 30% of the samples with residues below the limit of detection. The work task of mixing/loading incurred the greatest inhalation exposure with a maximum of 4.7 µg of exposure experienced by one mixer/loader during one workday.

The average daily exposure (dermal and inhalation) to bensulfuron methyl was: pilots-1.95 mg (range 0.50-2.76 mg), mixer/loaders-2.47 mg (range 0.94-3.62 mg) and flaggers-2.19 mg (range 0.30-3.93 mg). During the cleanup procedure, the pilots experienced an average of 1.1 mg of dermal exposure.

The average daily bensulfuron methyl exposure for each of the work tasks listed in Table 3 was: pilot-66 µg; mixer/loader-85 µg and flagger-72 µg per pound of a.i. applied. In order to use these values for estimating the exposure to fenoxaprop-ethyl from aerial applications some adjustments need to be made for the protective clothing worn in the Londax® study. The proposed Whip® label requires workers (pilots, mixer/loaders and flaggers) to wear work clothing (long-sleeved shirt and long pants, shoes and socks), chemical resistant gloves and protective eyewear. Workers mixing and loading Whip® may also need to wear an apron and use a closed system. The EPA Worker Protection Standard will require pilots to wear chemical resistant gloves when entering or leaving an aircraft contaminated with pesticide residues. California regulations also require the pilot to wear chemical resistant gloves when adjusting, cleaning or repairing contaminated mix, load and application equipment. In the Whip® ground applicator study (Orius Associates Inc., 1985), it was observed that chemical resistant gloves reduced fenoxaprop-ethyl exposure to the hands by 94%. To derive the average daily exposure to fenoxaprop-ethyl for workers making ground applications in Table 5 when gloves are worn, the hand exposures observed in Table 2 study were multiplied by 0.06 to correct for the protection provided by wearing gloves.

Pilots are required by the proposed Whip® label to wear chemical resistant gloves. Pilots wore leather or cotton gloves in the bensulfuron methyl exposure study and the protection provided by these materials is generally believed to be less than chemical resistant. As a result a correction needs to be made for the exposure to the hands of the pilots. This correction was made in Table 4 with exposure data from a study by Maddy *et al.*, (1984) that observed the exposure to the hands of pilots not wearing gloves represented approximately 54.5% of the total exposure.

The label rate for Whip® 1EC Herbicide on rice is 2.4-3.2 oz. of a.i. per acre with a minimum of 10 gallons of water per acre. In the bensulfuron methyl study, 333-538 acres of rice were treated per workday with a minimum of 5 gallons of water per acre. The higher minimum dilution rate for Whip® 1EC Herbicide can reduce the rice acreage by 33% that can be treated in a workday (Jones, 1993). This is due to the fact that fewer acres can be treated per load. By reducing the treated bensulfuron methyl acreage by 33%, the fenoxaprop-ethyl handled during the Whip® 1EC Herbicide applications would range from 33-72 lbs of a.i. per workday. Exposures in Table 5 were calculated based on the maximum application rate. These estimates of lbs a.i. applied per workday in conjunction with the daily exposure rates from the bensulfuron methyl study were used to derive the daily exposures to fenoxaprop-ethyl in Table 4 for the pilots, mixer/loaders and flaggers. These exposures are based on the maximum acres treated per day (360) and the maximum rate of fenoxaprop-ethyl applied (3.2 ozs a.i. per acre).

Tables 4 and 5 estimate the daily exposure and the seasonal average daily dosage for workers mixer/loading and applying fenoxaprop-ethyl and for workers flagging aerial applications based on 8 hours of exposure per workday. These formulas were used to calculate the various levels of occupational exposure.

Total Daily Exposure (mg/person/8-hour day) = directly estimated from dosimeters placed underneath the protective clothing and observed inhalation exposure.

Absorbed Daily Dosage, ADD (µg/kg/day) = (Daily Dermal Exposure x % dermal absorption) + (Inhalation Exposure x % absorption) x 1,000 µg/mg ÷ weight (male 76 kg).

Seasonal Average Daily Dosage, SADD (µg/kg/day) = ADD x days exposed/number of days per use season.

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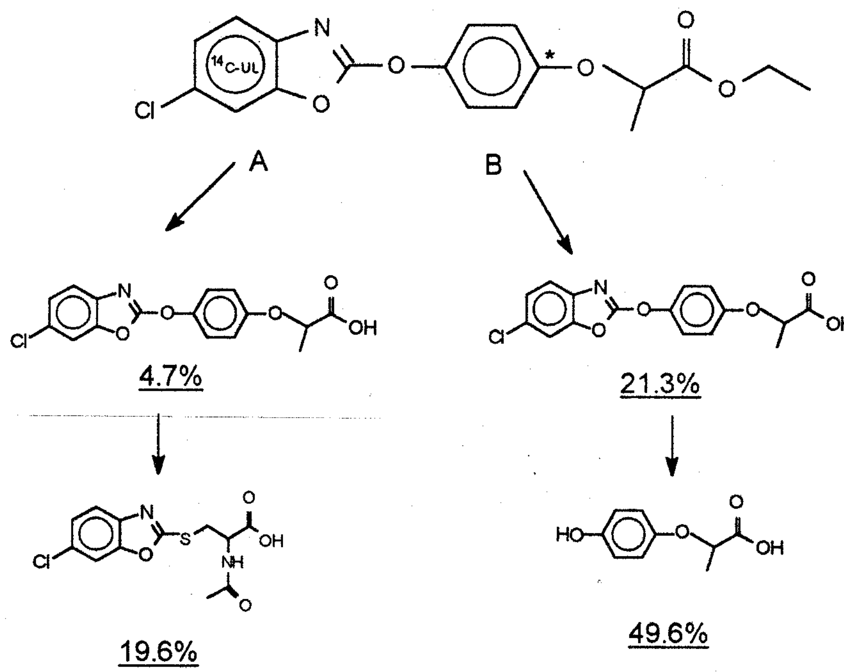
FIGURE 1. The Pathway for Urinary Metabolites of 14C Fenoxaprop-Ethyl

Labeled in the Chlorophenyl-U Position (A) and the Dioxyphenyl- I Position (B)a,b.



a. Female rats were given a single oral dose of 2 mg/kg b.w. of 14C fenoxaprop-ethyl and the urinary excretion was collected for 96 hours. Rats dosed with the 14C label in the chlorophenyl-U position (Dorn *et al.,* 1985) had 54 % of the dose recovered in the urine. Rats dosed with the label in the dioxphenyl-I position (Burkle et *al.,* 1985) had 71% of the dose recovered in the urine.

b. The percentage values represent the percent of the dose that was excreted as the noted metabolite in urine. The parent material was not detectable in the urine.

Table 1. The Average Percent of a Dermal Dose Absorbed by Rats After a Ten Hour Exposure to Radio-Labeled Fenoxaprop-Ethyl

GROUP No.	APPLIED DERMAL DOSE (µg)	FENOXAPROP-ETHYL DETECTED TISSUES(a) (µg)	CARCASS (µg)	EXCRETA(b) (µg)	SKIN SITE(c) (µg)	% OF DOSE ABSORBED
I.	21.9	0.77	1.19	0.34	13.9	73
II.	213	3.04	5.75	1.79	122	62
Ill.	1,894	10.7	23.0	10.0	771	43
IV.	23,658	150	94.4	49.3	16,482	70

Haskell, WH&S, 1993.

(a) Tissues are the blood, fat, kidney, liver, ovaries and uterus,
(b) Urine and feces.
(c) The skin at the application site and the skin adjacent to the rubber ring that protected the application site.

Table 2. The Average Daily Exposure to Fenoxaprop-Ethyl For Mixer/Loaders and Applicators Making Ground Applications to Soybeans

WORK TASK (worker #)	AVERAGE DAILY FENOXAPROP-ETHYL EXPOSURE (a,b) (µg of exposure/lb of a.i. applied)					LBS A.I. APPLIED PER WORKDAY	TOTAL DAILY EXPOSURE (c) (mg)
	foam filter	hand wash	face/neck	lower/upper body	total		
Mix/Load/Apply and Clean							
operator A	3.50	36.3	2.0	4.0	45.8	9.25	0.42
operator 6	1.80	293	3.0	5.0	303	8.03	2.43
operator C*	1.20	2173	26.0	36.0	2236	12.05	27.2
AVERAGE	2.17	834	10.3	15.0	862	9.8	10.0

Haskell, WH&S, 1993

*Operator C repaired a broken hose that connected the two belly tanks on the tractor.

(a) The source of the data from the study (Orius Associates Inc., 1985) are: respiration (foam filters) - Table 5, hand wash-Tables 8 and 9, face/neck-Tables 28, 32 and 36, and lower/upper body-Tables 28, 32 and 36.
(b) The exposure estimate when workers wore long pants, a long-sleeved shirt and no chemical resistant gloves.
(c) The TOTAL DAILY EXPOSURE (mg) was calculated as the total AVERAGE DAILY FENOXAPROP-ETHYL EXPOSURE (µg) per lb a.i. applied multiplied by the AVERAGE LBS A.I. APPLIED PER WORKDAY divided by 1000 (µg/mg).

The Whip 1 EC Herbicide label requires operators mixing fenoxaprop-ethyl to wear chemical resistant gloves. The exposure mitigation provided by the gloves can be estimated by multiplying the value in Table 8 of the study (Orius Associates Inc., 1985) for exposure to both hands (ug a.i./lb a.i.) of each worker by 94% (% protection observed in the study for gloves). This value subtracted from the value for the hand wash will provide an estimate of exposure to the hands when chemical resistant gloves are worn.

Table 3. The Average Daily Exposure to Bensulfuron Methyl For Mixer/Loaders and Applicators Making Applications to Rice

WORK TASK (worker #)	AVERAGE DAILY BENSULFURON METHYL EXPOSURE [(a,b)] (µg of exposure/lb of a.i. applied)							AVERAGE LBS A.I. APPLIED PER WORKDAY	TOTAL DAILY EXPOSURE [(c)] (mg)
	foam filter	hand wash	face/neck	arms	upperbody	lower body	total		
Pilots									
site 1	0.66	18.5	3.2	22.6	12.1	38.9	96.0	28.7	2.76
site 2	0.12	4.3	0.5	7.4	3.0	4.1	19.4	25.7	0.50
site 3	0.58	14.0	3.0	50.9	8.9	19.9	97.3	26.6	2.59
AVERAGE	0.42	11.5	2.1	25	7.5	19.3	66	27	1.95
Mixer/Loaders									
site 1	1.07	256	3.7	62.7	8.8	24.3	126.2	28.7	3,62
site 2	0.56	5.4	1.6	25.4	1.7	2.0	36.7	25.7	0.94
site 3	1.54	29.9	4.0	43.1	9.4	19.6	1075	26.6	2.86
AVERAGE	1.01	18.8	3.0	41.9	6.1	14.0	85.0	27	2.47
Flaggers									
site 1	0.70	27.1	16.3	67.0	14.2	13.0	138.3	28.7	3.93
site 2	0.20	1.4	1.3	5.9	2.0	0.8	11.6	25.7	0.30
site 3	0.45	6.9	3.5	34.1	6.6	36.1	87.7	26.6	2.33
AVERAGE	0.43	10.7	6.5	32.7	7.0	15.1	72.0	27	2.19

Haskell, WH&S, 1993

(a) Each value represents the average amount of Londax® found on each sample matrix for those workdays at the site.
(b) The "AVERAGES" take into account three consecutive workdays at sites 1 and 3 and four consecutive workdays at site 2.
(c) The TOTAL DAILY EXPOSURE (mg) was calculated as the total AVERAGE DAILY LONDAX EXPOSURE (ug) per *lb* a.i. applied multiplied *by* the AVERAGE LBS A,I. APPLIED PER WORKDAY divided by 1000 (µg/mg).

Table 4. Estimated Exposure for Pilots, Mixer/loaders, and Flaggers as Mitigated by the Whip® 1EC Label[a]

	Pre-Mitigation µg/lb a.i. applied			Post Mitigation[(d)] µg/lb a.i. applied		
Task	Body	Hands	Inhalation	Body	Hands	Inhalation
Pilot	54 (56)	65[(b)] (67)	0.37 (0.44)	54 (56)	3,9[(e)] (4.0)	0.37 (0.44)
Mixer/Loader	65 (34)	19[(c)] (13)	1.0 (0.70)	3.3[(f)] (1.7)	19 (13)	0.10 (0.035)
Flagger	62 (52)	11 (13)	0.43 (0.41)	62 (52)	0.64[(e)] (0.76)	0.43 (0.41)

(a) The exposure data was derived from the results of the bensulfuron-methyl study in Table 3. The arithmetic mean and standard deviation ( ) of 9 or 10 individuals for each work task are shown.

(b) The pilots wore cotton or leather gloves during the study. However, the bensulfuron-methyl label does not require the pilots to wear gloves. A study by Maddy et al., (1984) indicates that exposure to the hands of pilots not wearing gloves represents 54.5% of the total exposure. The observed exposures in the study were corrected with the following equation: X/0.455-X = Y where X equals the body exposure except hands and Y equals the corrected exposure to the hands.

(c) The mixer/loaders wore wearing chemical resistant gloves during the study.

(d) Mitigation provided by fenoxaprop-ethyl label is different than the surrogate exposure study (bensulfuron methyl).

(e) Chemical resistant gloves were observed to reduce exposure to fenoxaprop-ethyl by 94%. Values were multiplied by 0.06.

(f) The whole body protection provided when workers wear either work clothing underneath a chemical resistant suit and chemical resistant gloves or wear work clothing, chemical resistant gloves and use a closed system to mix and load is 95%. The values have been multiplied by 0.05.

Table 5. Estimate for Mitigated Daily and Seasonal Exposure to Fenoxaprop-Ethyl for Pilots, Mixer/loaders, and Flaggers Making Applications to Rice

Work Task	Average Daily Exposure[(a,b)] (µg/lb of a.i. applied) Dermal	Inhalation	lbs of Active Ingredient Applied per Workday[(c)]	ADD[(d)] (µg/kg/day)	SADD[(e,f)] (µg/kg/day)
Aerial Application:					
Pilot					
mean (arth.)	58	0.37	72	40	17
(+1 SD)	120	0.81	72	83	---
(+2 SD)	180	1.3	72	130	---
Mixer/loader					
mean (arth.)	22	0.10	72	26	11
(+1 SD)	37	0.14	72	36	---
(+2 SD)	52	0.17	72	46	---
Flagger					
mean (arth.)	63	0.43	72	44	19
(+1 SD)	120	0.84	72	83	---
(+2 SD)	170	1.3	72	120	---
Ground Application:					
Mix/Load/Apply					
and Clean-low	----	----	----	1.0	0.29
-high	----	----	----	22	6.3

(a) The value for the Average Daily Fenoxaprop-Ethyl Exposure for each work task was taken from Table 4.

(b) The exposure estimate when workers wear long pants and long-sleeved shirt and chemical resistant gloves and the mixer/loader uses a closed mixing/loading system. Fifteen µg/lb a.i. of dermal exposure has been added to the mixer/loader from cleaning the airplane.

(c) The fenoxaprop-ethyl acreage treated by air is equivalent to the acreage treated in bensulfuron-methyl study (538 acres per workday) reduced by 33% to reflect the greater minimum dilution rate (10 gallons per acre) for applications to rice and the label rate of 3.2 oz. a.i. per acre for Whip® 1EC Herbicide.

(d) The Absorbed Daily Dosage (ADD) includes material from dermal and inhalation exposure. The percent of dermal absorption is 73%. Inhalation uptake is assumed to be 50% with 100% absorption (Raabe, 1988). The applicator exposure studies were conducted on male workers and the assumed body weight was 76 kg.

(e) The ADD multiplied by the annual number of exposure days, then divided by the season of use- 35 days. Exposure days:
1. Aerial application- 15 days (Jones, 1993).
2. Ground application- 10 days (Haskell, 1993).

(f) Since the subchronic toxic effect may occur only after a series of exposures, the mean value alone is appropriate for calculating the Seasonal Absorbed Daily Dosage (SADD).